Final approval of the article: RD, JW, AP, AZ, BS, DW
Statistical analysis: RD, JW
Obtained funding: Not applicable
Overall responsibility: RD

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Submitted Jun 27, 2011; accepted Sep 24, 2011.

Additional material for this article may be found online at www.jvascsurg.org.

DISCUSSION

Dr Joseph Ricotta (*Atlanta, Ga*). How long were these patients anticoagulated for? Was there variability between the studies in terms of the duration of anticoagulation therapy?

Dr Randall R. De Martino. There was some variation. We required a minimum of 30 days because most of these were postoperative patients and that is what reporting goes to, although I think treatment should last for at least 6 weeks. We did a sensitivity analysis of outcomes by studies reporting 6 weeks of anticoagulation treatment or less. There was no change in the effect on clot propagation or PE.

Dr Ricotta. The longer the duration?

Dr De Martino. Correct.

Dr James Debord (*Peoria, Ill*). Do you think your analysis and results can be extrapolated to isolated gastrocnemius and soleus plexus clots in the absence of the named tibial vessel clots?

Dr De Martino. We did not look specifically at gastrocnemius or soleal clots in this study. We were focused on tibial and peroneal thrombi. I think that they may follow a similar pattern, although we can't make any conclusions based on this study. Other studies that have addressed that question and maybe a compilation of those studies can help identify if they are similar in characteristics. But I don't know that the clinical history of them is as well defined as is tibial and peroneal.

Dr Firas Mussa (*New York, NY*). Your last bullet suggests future studies. Can you elaborate on design of those studies?

Dr De Martino. I think there is still clinical equipoise as to whether or not we can treat or not treat these patients. Based on

the data and the studies that are available, I think that there is still a debate about this. I think clinical randomized trials will need to assess the benefits and the harms of treatment, including bleeding, mortality rates, and post-thrombotic syndrome. I am aware of one ongoing clinical study in Europe, but I am unaware of the current enrollment status. I was told yesterday in discussion, the University of Washington has applied for a grant to perform a randomized trial for this, and we hope that that will be funded and shed light on this topic.

Dr Cynthia Shortell (*Durham, NC*). It is no surprise that anticoagulation prevents thrombotic complications of calf vein clot. The question has always been, when is the risk of anticoagulation worth the benefit? And in calf vein thrombosis, that issue gets down to what the risks of those patients are. One would intuit that high-risk patients with calf clots, such as neurosurgical patients or immobile patients, would be at higher risk, but that's unknown at this point. Did any of the studies that you included contain that information? And if so, do you think you could use it to help us identify those patients with calf clot that would really benefit from anticoagulation?

Dr De Martino. I think we agree that there are patients who are at higher risk. Several of these studies did try to identify specific risk factors that would identify those patients with thrombi that are going to propagate or cause PE. The most consistent risk factor identified was inpatient status. Many other patient-level variables that they were able to analyze were not predictive in their analyses. We didn't include that type of review in the present study, but that is what I have been able to extract from the data that is available to date.

Dr Mark Meissner (*Seattle, Wash*). I was somewhat surprised that although bleeding was heterogeneous, pulmonary embolism and thrombus propagation was remarkably homogeneous. I think this is surprising, because perhaps even more so than with proximal vein thrombosis, calf vein thrombosis is often perceived to be a heterogeneous disease with the risk of complications based on the underlying risk factors for thrombosis. Your analysis seems to imply that all calf vein thrombi should be treated as equal, which may not be correct. Can you explain the homogeneity of your findings?

Dr De Martino: In regards to PE and clot propagation, I think our pooled summary was homogeneous because of our strict entry criteria. There are other studies reported on calf DVT that were excluded because they didn't meet this criteria. I think that helped in creating a homogeneous estimate.

The majority of studies did report on PE and clot propagation. Very few studies reported bleeding and mortality complications, so the data that we were able to extract were sparse and spread across eight studies, where only two to three may have contributed to the data, and I think that that affected our ability to make a homogeneous summary effect.

I think that while we were able to make a homogeneous study effect, we acknowledge that the strength of our findings comes from the quality of the studies that they were derived from. And so a robust clinical trial will really answer this question in the best light possible.

Dr Peter Gloviczki (*Rochester, Minn*). Did you notice a difference in symptomatic and asymptomatic calf vein thrombosis, or were all these patients symptomatic?

Dr De Martino. We didn't perform a formal subgroup analysis of studies that were symptomatic or asymptomatic. Approximately half of the studies identified their patients as symptomatic, two of those four being the randomized controlled trials. But we are unable to make a comment about whether the symptomatic status does make a difference.

Dr Gloviczki. And was the diagnosis of PE made using similar techniques in these studies?

Dr De Martino. The diagnosis of PE was similar in all but one study, which used a combination of V/Q scan and clinical diagnosis based on patients with a sudden death that was preceded by rapid leg swelling. And so it was felt that that was a clinical diagnosis of PE and we did include that.

Dr Roger Shinnerl (*Evansville, Ind*). I was wondering if you could please tell me if I am wrong, but I was left with the distinct impression, after looking at your data briefly, that all of the positive results were out of one study, the Pellegrini study. And that disturbs me. Does that not make that study an outlier? And even if not, should we really be endorsing that finding with the results of a pooled analysis?

Dr De Martino. That one study was a nested case-control study within a randomized trial. While they did identify a lot of outcomes, I do not think that their methods were any different than the other randomized trial that would make me think that they should be excluded or be an outlier. I think the fact that our summary of facts remained homogeneous despite their inclusion attests that it was appropriate to include them within our analysis.